ANSWER 28 OF 31 MEDLINE on STN

AN 97010891 MEDLINE

DN PubMed ID: 8857924

TI Contrasting effects of plasminogen activators, urokinase receptor, and LDL receptor-related protein on smooth muscle cell migration and invasion.

AU Okada S S; Grobmyer S R; Barnathan E S

CS University of Pennsylvania School of Medicine, Philadelphia 19104-6060, USA.

NC HL02870 (NHLBI)
HL47839 (NHLBI)

SO Arteriosclerosis, thrombosis, and vascular biology, (1996 Oct) Vol. 16, No. 10, pp. 1269-76.
Journal code: 9505803. ISSN: 1079-5642.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LA English

FS Priority Journals

EM 199611

ED Entered STN: 19 Dec 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 20 Nov 1996

AB Smooth muscle cell (SMC) migration is an early response to vascular injury and contributes to the development of intimal thickening. Upregulation of several components of the plasminogen activator (PA) system has been documented after vascular injury. Utilizing a Transwell filter assay system and human umbilical vein SMCs, we sought to define the role of four different PA system components on SMC migration and matrix invasion: (1) PAs, (2) plasmin, (3) PA receptors, and (4) PA clearance receptors (ie, low density lipoprotein receptor-related protein [LRP]).
Addition of active two-chain urokinase-type PA (UPA) stimulated random migration (192 +/- 30% of control, 0.36 nmol/L, P < .001). The stimulation was inhibited by pretreatment with diisopropylfluorophosphate, PA inhibitor type 1 (PAI-1), or aprotinin, a plasmin inhibitor. Augmented migration was also observed with either low-molecular-weight UPA or the amino terminal fragment of UPA (ATF), with the effects being additive. Stimulation by ATF alone, however, was not inhibited by aprotinin. The stimulatory effect was not specific for UPA, in that tissue-type PA (TPA) also increased migration (169 +/- 9% of control, 10 nmol/L, P < .001); the augmentation was inhibited by pretreatment with DFP, PAI-1, or aprotinin and was additive to the UPA effect. Antibodies to the UPA receptor but not 5'-nucleotidase (another glycosylphosphatidylinositol-anchored cell surface protein) inhibited baseline and UPA-stimulated migration. Similarly, both UPA and TPA stimulated invasion of a collagen gel; this augmentation was inhibited by aprotinin, whereas antibodies to the UPA receptor reduced baseline invasion. Finally, we tested whether inhibition of LRP function, which mediates internalization of PA/inhibitor complexes, affected either process. Both antibodies to LRP and recombinant receptor associated protein, a known inhibitor of ligand binding to the LRP, significantly inhibited migration but did not affect collagen gel invasion. These data demonstrate the ability of several components of the PA system to modulate SMC migration and invasion in vitro via plasmin-dependent and -independent mechanisms.

ANSWER 29 OF 31 MEDLINE on STN

AN 94253176 MEDLINE

DN PubMed ID: 7515061

TI Molecular dissection of ligand binding sites on the low density lipoprotein receptor-related protein.

AU Willnow T E; Orth K; Herz J

CS Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas 75235.

NC HL 20948 (NHLBI)

SO The Journal of biological chemistry, (1994 Jun 3) Vol. 269, No. 22, pp. 15827-32.
Journal code: 2985121R. ISSN: 0021-9258.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LA English

FS Priority Journals

EM 199406

ED Entered STN: 7 Jul 1994
Last Updated on STN: 3 Mar 2000
Entered Medline: 30 Jun 1994

AB The low density lipoprotein receptor-related protein (LRP) is a large multifunctional receptor that is involved in the cellular uptake of a number of functionally diverse ligands including apoE-rich remnant lipoproteins, lipoprotein lipase, alpha 2-macroglobulin-protease complexes, plasminogen activator-inhibitor complexes, and the active protease tissue-type plasminogen activator. Ligand binding and competition experiments suggest that most LRP ligands bind to specific, independent sites on the large 515-kDa subunit of the receptor. In a previous study (Moestrup, S.K., Holtet, T.L., Etzerodt, M., Thogersen, H.C., Nykjaer, A., Andreasen, P.A., Rasmussen, H.H., Sottrup-Jensen, L., and Gliemann, J. (1993) J. Biol. Chemical 268, 13691-13696), ligand blotting was used to localize the binding sites for urokinase-type plasminogen activator-plasminogen activator inhibitor-1 (PAI-1) complexes and for alpha 1-macroglobulin to a proteolytic fragment of LRP containing the second cluster of complement-type cysteine-rich repeats. Here, we have used a recombinant DNA approach to express functionally restricted chimeric "LRP-minireceptors" containing two different regions of the extracellular domain of the receptor in cultured cells. Receptor-associated protein, a negative modulator of LRP activity, is bound and internalized by cells transfected with either construct. A minireceptor containing the cluster of eight complement-type cysteine-rich repeats followed by four epidermal growth factor precursor homologous domains binds and internalizes 125I-labeled plasminogen activator-PAI-1 complexes. It also mediates the cellular uptake of the uncomplexed protease tissue-type plasminogen activator (tPA), suggesting that the tPA and PAI-1 binding sites on LRP are in close vicinity and might promote cooperative binding of tPA-PAI-1 complexes. However, alpha 2-macroglobulin is not internalized by this minireceptor suggesting that this ligand requires the presence of a single epidermal growth factor-repeat which is contained in the previously studied proteolytic fragment but is absent from the minireceptor.

ANSWER 26 OF 31 MEDLINE on STN
AN 97147643 MEDLINE
DN PubMed ID: 8994415
TI Antagonists of the mannose receptor and the LDL receptor-related protein dramatically delay the clearance of tissue plasminogen activator.
AU Biessen E A; van Teijlingen M; Vietsch H; Barrett-Bergshoeff M M; Bijsterbosch M K; Rijken D C; van Berkel T J; Kuiper J
CS Division of Biopharmaceutics, Leiden/Amsterdam Center for Drug Research, University of Leiden, The Netherlands.
SO Circulation, (1997 Jan 7) Vol. 95, No. 1, pp. 46-52.
Journal code: 0147763. ISSN: 0009-7322.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199702
ED Entered STN: 19 Feb 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 4 Feb 1997
AB BACKGROUND: Clinical application of tissue plasminogen activator (TPA) as a fibrinolytic agent is complicated by its rapid clearance from the bloodstream, which is caused by TPA liver uptake. The mannose receptor on endothelial liver cells and the LDL receptor-related protein (LRP) on parenchymal liver cells were reported to contribute to liver uptake. METHODS AND RESULTS: In this study, we addressed whether TPA clearance can be delayed by inhibiting receptor-mediated endocytosis of TPA. A series of cluster mannosides was synthesized, and their affinity for the mannose receptor was determined. A cluster mannoside carrying six mannose groups (M6L5) displayed a subnanomolar affinity for the mannose receptor (Ki = 0.41 +/- 0.09 nmol/L). Preinjection of M6L5 (1.2 mg/kg) reduced the clearance of 125I-TPA in rats by 60% because of specific inhibition of the endothelial cell uptake. The low toxicity of M6L5, combined with its accessible synthesis and high specificity for the mannose receptor, makes it a promising agent to improve the pharmacokinetics of TPA. Blockade of LRP by 39-kD receptor-associated protein (GST-RAP) also inhibited TPA clearance by 60%. Finally, combined preinjection of M6L5 and GST-RAP almost completely abolished reduced liver uptake of TPA and delayed its clearance by a factor of 10. CONCLUSIONS: It can be concluded that (1) the mannose receptor and LRP appear to be the sole major receptors responsible for TPA clearance and (2) therapeutic levels of TPA can be maintained for a prolonged time span by coadministration of the aforementioned receptor antagonists.

ANSWER 24 OF 31 MEDLINE on STN
AN 97442468 MEDLINE
DN PubMed ID: 9295345
TI Soluble low density lipoprotein receptor-related protein (LRP) circulates in human plasma.
AU Quinn K A; Grimsley P G; Dai Y P; Tapner M; Chesterman C N; Owensby D A
CS Center for Thrombosis and Vascular Research, University of New South Wales, Sydney 2052, Australia.
SO The Journal of biological chemistry, (1997 Sep 19) Vol. 272, No. 38, pp. 23946-51.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 5 Nov 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 23 Oct 1997
AB Our studies have identified a soluble molecule in normal human plasma and serum with the characteristics of the alpha-chain of the low density lipoprotein receptor-related protein (LRP). LRP is a large multifunctional receptor mediating the clearance of diverse ligands, including selected lipoproteins, various protease inhibitor complexes, and thrombospondin. A soluble molecule (sLRP) has been isolated from plasma using an affinity matrix coupled with methylamine-activated alpha2-macroglobulin, the ligand uniquely recognized by LRP, and eluted with EDTA. This eluate contains a protein that co-migrates on SDS-polyacrylamide gel electrophoresis with authentic human placental LRP alpha-chain, is recognized by anti-LRP alpha-chain monoclonal antibodies, and binds the 39-kDa receptor-associated protein (RAP) and tissue plasminogen activator-inhibitor complexes. A similar RAP-binding molecule was detected in medium conditioned for 24 h by primary cultures of rat hepatocytes, suggesting that the liver may be the in vivo source of sLRP. In contrast, immunoprecipitation experiments failed to detect the production of sLRP by cultured HepG2 hepatoma and primary human fibroblast cells. Addition of a soluble form of LRP to cultured HepG2 cells resulted in a significant inhibition of capacity of these cells to degrade tPA, a process that has been demonstrated to be mediated by cell surface LRP. Preliminary data indicate that the concentration of sLRP is altered in the plasma of patients with liver disease. Increased levels of sLRP may antagonize the clearance of ligands by cell bound LRP perturbing diverse processes including lipid metabolism, cell migration and extracellular proteinase activity.

ANSWER 22 OF 31 MEDLINE on STN

AN 1998272516 MEDLINE

DN PubMed ID: 9610960

TI Low density lipoprotein receptor-related protein (LRP) expression varies among Hep G2 cell lines.

AU Grimsley P G; Quinn K A; Chesterman C N; Owensby D A

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SO Thrombosis research, (1997 Dec 15) Vol. 88, No. 6, pp. 485-98. Journal code: 0326377. ISSN: 0049-3848.

CY United States

DT (COMPARATIVE STUDY) Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LA English

FS Priority Journals

EM 199808

ED Entered STN: 17 Aug 1998
Last Updated on STN: 20 Apr 2002
Entered Medline: 6 Aug 1998

AB The multiligand receptor, low density lipoprotein receptor-related protein (LRP), is implicated in processes such as atherosclerosis and fibrinolysis through its mediation of the catabolism of lipoproteins, proteases, and protease inhibitor complexes. The hepatoma cell line Hep G2 expresses LRP and has been used widely to investigate the catabolism of LRP ligands including tissue-type plasminogen activator (tPA). However, the mechanism and degree by which tPA interacts with Hep G2 has been reported with some inconsistencies which may reflect variation in their level of LRP expression. To address this possibility we characterized, antigenically and functionally, LRP expression in high and low passage Hep G2 cells both from the parental line (ATCC sourced) and a cloned subline, a16. The LRP contribution to 125I-tPA binding varied from 65% for high passage a16 cells, to 20% for low passage parent cells as quantified by inhibition in the presence of 39-kD receptor associated protein (RAP) which prevents binding of all known LRP ligands. The same trend in LRP expression among Hep G2 sublines was further evident in their ability to degrade 125I-tPA and survive Pseudomonas exotoxin A challenge. These results imply wide variability in basal LRP expression among Hep G2 lines dependent on cell lineage and long-term culture conditions.

ANSWER 20 OF 31 MEDLINE on STN

AN 2000098928 MEDLINE

DN PubMed ID: 10632583

TI Role of tissue plasminogen activator receptor LRP in hippocampal long-term potentiation.

AU Zhuo M; Holtzman D M; Li Y; Osaka H; DeMaro J; Jacquin M; Bu G

CS Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri 63110, USA.

NC AG13956 (NIA)
NS37525 (NINDS)

SO The Journal of neuroscience : the official journal of the Society for Neuroscience, (2000 Jan 15) Vol. 20, No. 2, pp. 542-9.
Journal code: 8102140. E-ISSN: 1529-2401.

CY United States

DT (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LA English

FS Priority Journals

EM 200002

ED Entered STN: 18 Feb 2000
Last Updated on STN: 21 May 2001
Entered Medline: 9 Feb 2000

AB The low-density lipoprotein (LDL) receptor-related protein (LRP) is a multifunctional endocytic receptor that is expressed abundantly in neurons of the CNS. Both LRP and several of its ligands, including tissue plasminogen activator (tPA), apolipoprotein E/lipoproteins, alpha(2)-macroglobulin, and the beta-amyloid precursor protein, have been implicated in various neuronal functions and in the pathogenesis of Alzheimer's disease. It has been reported that induction of tPA expression may contribute to activity-dependent synaptic plasticity in the hippocampus and cerebellum. In addition, long-term potentiation (LTP) is significantly decreased in mice lacking tPA . Here we demonstrate that tPA receptor LRP is abundantly expressed in hippocampal neurons and participates in hippocampal LTP. Perfusion of hippocampal slices with receptor-associated protein (RAP), an antagonist for ligand interactions with LRP, significantly reduced late-phase LTP (L-LTP). In addition, RAP also blocked the enhancing effect of synaptic potentiation by exogenous tPA in hippocampal slices prepared from tPA knock-out mice. Metabolic labeling and ligand binding analyses showed that both tPA and LRP are synthesized by hippocampal neurons and that LRP is the major cell surface receptor that binds tPA. Finally, we found that tPA binding to LRP in hippocampal neurons enhances the activity of cyclic AMP-dependent protein kinase, a key molecule that is known to be involved in L-LTP. Taken together, our results demonstrate that interactions between tPA and cell surface LRP are important for hippocampal L-LTP.